Expanded Combined Test and Contingent Strategy

In our study, the most remarkable advantage of adding ultrasound markers to the combined test, either to the entire or only to intermediate risk population, is a 29 or 33% FPR reduction. Regarding the expanded combined test, an improved screening efficacy has been reported in previous studies, obtaining both an increased DR and a reduced FPR (10–29%) [15, 25]. In our series, only the addition of DV or NB ± DV to the combined test resulted in a reduction of FPR by about one fourth (25–29%), similar to that reported in a previous study [14]. Concerning the contingent screening approach, in our series the use of DV ± TF resulted in a significant 42% FPR reduction (from 6.9 to 4.0%) with a marginal DR increase. Similarly, in most of the reported series, greater FPR reductions were achieved in the contingent approach as compared to the expanded combined [5, 11, 12], although the DR may decrease [12]. The main advantage of the contingent approach is that additionally marker assessment is required only in about 10% of pregnancies, being considered the most cost-effective screening strategy in most of the studies [26]. A serious drawback of contingent screening was recently demonstrated by our group, when largely applied in public Catalan health service, because half of the pregnancies with low intermediate risks could not be offered the second stage before 14 weeks due to time constraints [11].

Weakness and Strengths of the Study

Weaknesses of our study limiting the applicability of our results to other centers are related to the characteristics of the study population, since 10% of our study population was at high risk for fetal aneuploidy. However when LRs were recalculated in the subgroup of unselected pregnancies (49 trisomies 21 among 9,685 pregnancies), no major differences were observed (data not shown). A second limitation of our study is the low success rates for NB (76%) and TF (71%) assessment, supporting that each center should decide either in which marker to be included and the strategy elected according to their own experience, economic budget and cost-effectiveness of the strategy. A third limitation is related to the method for LR computation not taking into account changes with gestational age and the interrelation between markers. This can be solved with the use of a proper software, but the aim of our study was to apply to first trimester ultrasound markers the same simplified method proposed by Nicolaides [20, 21] for second trimester ultrasound markers.

The main strength of our study is the high external reproducibility. as all the routine scans were performed by

Table 2. Detection and False Positive Rates (with 95% confidence intervals) achieved with the addition of NB, DV and TF to the combined test risk either in the entire study population (expanded combined test) or in the intermediate risk group (contingent strategy)

		Detection rate	False positive rate
None (combined test)	Rate 95% CI	92% (93/101) 87–97	6.9% (769/11,160) 6.4–7.4
Expanded combined test	Rate 95% CI	89% (87/98) 83–95	4.9% (542/11,050) 4.5–5.3*
Contingent screening	Rate 95% CI	91% (92/101) 86–97	4.6% (551/11,142) 4.5–5.4*
Different marker combinations for an expanded combined test			
NB	Rate 95% CI	92% (71/77) 86–98	6.5% (557/8,506) 6.0–7.1
DV	Rate 95% CI	92% (86/93) 87–98	5.2% (565/10,830) 4.8–5.6*
TF	Rate 95% CI	94% (33/35) 87–100	13% (140/1,078) 11.0–15.0
NB + DV	Rate 95% CI	93% (67/72) 87–99	4.9% (406/8,289) 4.4–5.4*
NB + TF	Rate 95% CI	96% (27/28) 90–100	12% (93/779) 9.7–14.2
DV + TF	Rate 95% CI	88% (30/34) 77–99	8.4% (88/1,053) 6.7–10.0
NB + DV + TF	Rate 95% CI	89% (24/27) 77–100	9.9% (75/760) 7.8–12.0
Different marker combinations for a contingent screening			
NB	Rate 95% CI	93% (92/99) 88–98	5.6% (604/10,766) 5.2–6.0*
DV	Rate 95% CI	93% (93/100) 88–98	4.7% (526/11,099) 4.3–5.1*
TF	Rate 95% CI	96% (90/94) 92–100	4.3% (423/9,924) 3.9–4.7*
NB + DV	Rate 95% CI	94% (92/98) 89–99	4.2% (452/10,726) 3.8–4.6*
NB + TF	Rate 95% CI	97% (90/93) 93–100	3.9% (388/9,881) 3.5–4.3*
DV + TF	Rate 95% CI	96% (90/94) 92–100	4.0% (399/9,914) 3.6–4.4*
NB + DV + TF	Rate 95% CI	97% (90/93) 93–100	4.0% (396/9,875) 3.6–4.4*

* Not overlapping confidence intervals when compared with the Combined test.

NB = Nasal bone; DV = ductus venosus; TF = tricuspid flow.

18 sonologists with different expertise and motivation. Contrary to the reported studies coming from relatively high risk groups as well as highly specialized operators such as FMF-associated authors, our study present 'real world' data from a large general screening practice with a mix of expertise among the operators, being more applicable to many screening practices.

Conclusions

Our study suggests that applying the NB, DV and TF likelihood ratios to the combined test risk, either in an expanded or contingent strategy, result in a significant FPR reduction. When NB, DV and TF combinations are applied to intermediate risks nearly half of the invasive procedures may be prevented.

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